## REMARKS

Claims 1-4, 7, 11-12, 16, 20 and 28 were pending in the application. Claims 1, 3-4, 7, 11, 16, 20 and 24 have been amended. Claim 2 has been canceled. Accordingly, upon entry of the amendments presented herein, claims 1, 3-4, 7, 11-12, 16, 20 and 24 will remain pending in the application.

Throughout the claims, the term "potentiating ratio" has been deleted.

Claims 1, 4 and 7 have been amended to specify that the method is for the treatment of lung cancer or pancreatic cancer.

Claims 1 and 4 have been amended to remove the word "effective."

Claims 1, 4 and 7 have been further amended, along with claims 11, 16 and 20, to specify that DMXAA or a pharmaceutically acceptable salt thereof and gemcitabine are administered "in a ratio in the range of 1:15 to 1:10."

Claim 7 has been further amended to replace the word "dosage" with the word "combination."

Claim 1 has been further amended to specify that the recited ratio refers to the ratio of DMXAA:gemcitabine.

Claims 4, 11, 16 and 20 have been further amended to specify that DMXAA or a pharmaceutically acceptable salt thereof is utilized "in an amount in the range of 500 to 4900 $mg/m^2$."

Claim 28 has been canceled.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any other Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

***Claim Objections***

Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully disagree. However, solely to expedite prosecution, claim 28 has been canceled. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claim 28 under 37 CFR 1.75(c).

***Claim Rejections – 35 USC § 112 – Second Paragraph***

Claims 2, 7, 11-12, 16 and 20 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Regarding claim 2, the Office contends that it is unclear whether the recited potentiating ratio refers to a ratio of DMXAA:gemcitabine or gemcitabine:DMXAA. Applicants respectfully disagree. However, solely to expedite prosecution, claim 1 has been amended to specify that the recited ratio refers to the ratio of DMXAA:gemcitabine. Support for this amendment is found at least, for example, at page 4, line 24, of the application as filed.

Regarding claim 7, the Office contends that the recitations of a pharmaceutical dosage comprising DMXAA or a pharmaceutically acceptable salt thereof "in an amount to provide a dosage range of 500 to 4900 mg/$m^2$" and gemcitabine "in a potentiating ratio in a mammal" are unclear with regard to the amount of each agent that is present in the composition. Applicants respectfully disagree. However, solely to expedite prosecution, claim 7 has been amended to specify that DMXAA or a pharmaceutically acceptable salt thereof is present in the composition "in a dosage in the range of 500 to 4900 mg/$m^2$." Support for this amendment is found at least, for example, at page 15, lines 23-24, and page 16, lines 1-10, of the application as filed. Claim 7 has also been amended to specify that gemcitabine is present in the composition with DMXAA or pharmaceutically acceptable salt thereof "in a ratio in the range of 1:15 to 1:10." Support for this amendment is found at least, for example, at page 4, lines 17-24, of the application as filed. As such, the amounts of the respective agents are clearly specified.

Regarding claims 7, 11-12, 16 and 20, the Office contends that the limitation "a potentiating ratio" does not define the amounts of DMXAA and gemcitabine present in the claimed formulations and kits. Applicants respectfully disagree. However, solely to expedite

prosecution, the term "potentiating ratio" has been deleted from all claims. Claims 11, 16 and 20 have been further amended to specify that DMXAA or a pharmaceutically acceptable salt thereof is present "in a dosage in the range of 500 to 4900 mg/m$^2$" with gemcitabine "in a ratio in the range of 1:15 to 1:10." Support for these amendments can be found at least, for example, at page 4, lines 17-24, page 15, lines 23-24, and at page 16, lines 1-10, of the application as filed. As such, the amounts of the respective agents are clearly specified.

At least for the foregoing reasons, Applicants request reconsideration and withdrawal of the rejection of claims under 35 U.S.C. § 112, second paragraph.

***Claim Rejections – 35 USC § 112 – First Paragraph***

Claims 1-4, 7, 11-12, 16, 20 and 28 stand rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Office contends that the specification does not reasonably convey that Applicants were in possession of the claimed "potentiating ratios." Applicants respectfully disagree. However, solely to expedite prosecution, claims 1, 7, 11, 16 and 20 have been amended to specify that DMXAA or a pharmaceutically acceptable salt thereof and gemcitabine are administered "in a ratio in the range of 1:15 to 1:10." Support for this amendment is found at least, for example, at page 4, lines 17-24, and in Example 2 of the application as filed.

With regard to the example provided in the Declaration of Hakin Djeha, filed March 23, 2009 (hereafter the "Djeha Declaration"), Applicants dispute the Office's conclusion that the combined drug effect of DMXAA and gemcitabine "was not greater than that of DMXAA alone" (see page 5 of the outstanding office action). Applicants maintain their position that the results presented in the instant application and the results presented in the Djeha Declaration clearly show surprising and unexpected results when using a combination of gemcitabine and DMXAA for the treatment of lung cancer tumors. As set forth in the second Declaration of Hakin Djeha, filed July 30, 2009, the difference in relative tumor volumes of the treatment groups is statistically significant and not merely additive. As such, the claimed DMXAA and gemcitabine combination therapy displays a synergistic effect.

Claims 1-3, 7 and 28 are further rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Office contends that the specification does not reasonably convey that Applicants were in possession of the claimed

"potentiating ratio." Applicants respectfully disagree. However, solely to expedite prosecution, the claims have been amended to delete the term "potentiating ratio." Applicants contend that reference to "a ratio in the range of 1:15 to 1:10" in the instant claims, as amended, is well supported, at least by the specification as filed (see, for example, page 4, lines 17-24, and Example 2).

Claims 1-3 and 28 are further rejected under 35 U.S.C § 112, first paragraph, on the grounds that the specification does not reasonably provide enablement for the treatment of all solid cancerous tumors with DMXAA and gemcitabine in a "potentiating ratio." Applicants respectfully disagree. However, solely to expedite prosecution, claims 1-3 have been amended, as discussed above, to specify a method for the treatment of lung cancer and pancreatic cancer, which comprises administration of DMXAA or pharmaceutically acceptable salt thereof in an amount in the range of 500-4900 $mg/m^2$ and gemcitabine, in a ratio in the range of 1:15 to 1:10. Support for these amendments can be found at least, for example, at page 4, lines 17-24, page 15, lines 23-24, page 16, lines 1-10, and at page 22 of the application as filed.

At least for the foregoing reasons, Applicants request reconsideration and withdrawal of the rejection of claims under 35 U.S.C § 112, first paragraph.

***Claim Rejections – 35 USC § 103***

Claim 4 stands rejected under 35 U.S.C § 103(a), as being unpatentable over Davis *et al.* (WO 00/48591) in view of Peters *et al.* (Pharmacology & Therapeutics, 2000, vol. 87, pages 227-253). Applicants respectfully disagree, at least for the reasons set forth in the response of July 30, 2009. However, solely to expedite prosecution, claim 4 has been amended to specify a method for the treatment of lung cancer and pancreatic cancer, which comprises administration of DMXAA or pharmaceutically acceptable salt thereof in an amount in the range of 500-4900 $mg/m^2$ and gemcitabine, in a ratio in the range of 1:15 to 1:10. Support for these amendments is found, at least, in the application as filed (see, for example, page 4, lines 17-24, page 15, lines 23-24, page 16, lines 1-10, and page 22, lines 24-26). It is Applicants' position that the claimed method is not obvious in view of Davis *et al.* or Peters *et al.*, alone or in combination.

Davis *et al.* teach combinations of DMXAA and nitric oxide synthase inhibitors, optionally used in further combination with any one of a list of anticancer agents, including antimetabolites, for the treatment of solid tumors. Davis *et al.* does *not* teach a combination

comprised solely of DMXAA and an antimetabolite, let alone a combination comprising DMXAA and gemcitabine. Moreover, Davis *et al.* does not teach the use of said combination for the treatment of lung cancer or pancreatic cancer, nor the specific dosage and ratio ranges specified in the claims as amended.

Peters *et al.* does not remedy this deficiency. Peters *et al.* teach that combinations of gemcitabine with other anticancer agents are useful for treating a variety of cancers. As set forth in the response of July 30, 2009, Peters *et al.* teach only combinations of gemcitabine with agents that have the similar mechanism of action as gemcitabine. As such, Peters *et al.* does not teach or suggest a combination with DMXAA, let alone the specific dosage and ratio ranges specified in the claims as amended.

The above arguments notwithstanding, Applicants dispute the Office's allegation of *prima facie* obviousness, on the grounds that the results presented in the instant application, as well as the results presented in the Djeha Declarations, clearly show surprising and unexpected results (*i.e.*, synergy) in using the claimed combination of gemcitabine and DMXAA for the treatment of pancreatic and lung cancer tumors. According to MPEP § 716.02(a)(I), evidence of a greater than expected result is evidence of non-obviousness, and furthermore, "evidence of a greater than expected result may... be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)." As previously set forth, the data of Example 2 of the specification, and the data of the Djeha Declarations, demonstrate that the combined drug effect on pancreatic and lung cancer tumors is greater than the sum of the effects of each individual agent. Furthermore, Applicants take the position that two anticancer agents cannot be expected, *a priori,* to display synergy in combination therapy solely by virtue of their individual usefulness, when abundant *a posteriori* knowledge informs otherwise (see, for example, Exhibit IV of the response of July 30, 2009). It follows that the synergy exhibited by the combinations of DMXAA and gemcitabine is unexpected, and to a non-obvious extent.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 4 under 35 U.S.C § 103(a).

## CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If there are any questions regarding the proposed amendments to the application, we invite the Examiner to call Applicants' representative at the telephone number below.

An extension of time and appropriate fee is being filed herewith. If any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. NVT-084USRCE3 from which the undersigned is authorized to draw.

Dated: April 21, 2010

Respectfully submitted,

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